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TITLE: Significance of Pathways Leading to RhoC Overexpression in Breast Cancer

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13. ABSTRACT (Maximum 200 Words)

Tumor biology is a recognized determinant of tumor behavior, including growth rate, motility and metastatic potential, and therapeutic resistance. This project was funded to investigate the regulation and expression of an excellent marker for aggressive breast tumors: RhoC-GTPase. When overactive, RhoC transforms mammary epithelial cells into a highly motile and invasive phenotype. We hypothesize that RhoC overexpression may be regulated by the transcription factor NF-kappa B and that at the same time RhoC is overexpressed the tumor also acquires therapy resistance. The objective of this study is to utilize existing breast cancer cohorts with tumor tissue and treatment response data available to assess the correlation between NF-kappa B and RhoC, individually and in combination, to treatment response.

The specific aims of the project are to determine 1) if RhoC and NF-kappa B are correlated; 2) if RhoC and NF-kappa B are associated, individually and in combination, with aggressive breast cancer; and 3) if NF-kappa B and RhoC are associated with therapy resistance.

Human subjects review was completed for the project the end of February 2005. Tumor array protocols have been written and pathological specimens are currently being collected. Subjects have been identified and recurrence information has been abstracted.

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INTRODUCTION

This study was funded to assess the relationship of RhoC and NF-kappa B to aggressive, metastatic, and therapy-resistant breast cancer. As more is learned about these tumor markers, the potential exists for improved clinical diagnosis, prognosis, and treatment. The purpose of the study is to understand the regulation of RhoC gene expression in an epidemiological setting, so that the clinical utility of RhoC as a tumor marker can be further evaluated and refined. A clear understanding of the genetic and cellular mechanisms involved in modulating the highly metastatic phenotype of this disease is expected to aid in diagnosis and treatment. The scope of this work includes the identification and collection of patient information from Henry Ford Health System (HFHS). HFHS is an integrated health system that offers a diverse, population-based patient population from which strong epidemiologic studies can be built. Patient information, including diagnostic and recurrence data, will be combined with gene expression data. Molecular and statistical analysis will occur in collaboration with the University of Michigan.

BODY

In the first 12 months of the project, we projected that we would finalize the study analysis plan and obtain the tumor tissue and outcome data from cohort resources. Below are the objectives from the original Statement of Work.

Task 1. To finalize study analysis plan

a. Conduct an updated literature review (Months 1-3)
b. Finalize Tumor Microarray (TMA) configuration (Month 4)
c. Submit required Institutional Review Board materials (Month 5)
d. Receive Institutional Review Board approval (Month 6)
e. Acquire needed antibodies for TMA (Months 5-6)

Task 2. To obtain the tumor tissue and outcome data from cohort resources

a. Operationalize cases of interest (Months 7-8)
b. Write a data manual with data specifications (Month 9)
c. Pull needed electronic data (Month 9)
d. Transfer (from Henry Ford Health System) consolidated tumor tissue specimens and case data from cohort resources to Merajver Laboratory (Months 10-12)

We have conducted and completed all of the above except for transferring the tumor tissue to the Merajver Laboratory at the University of Michigan. We could not begin this process until final USAMRMC review was completed and approved. Given that this occurred in February 2005, we have not had sufficient time to finish identifying and retrieving the tumor blocks from the tissue archive. We expect that this process will be completed within the next 3-4 months, as it is ongoing and we are making speedy progress toward this goal.

KEY RESEARCH ACCOMPLISHMENTS

The study is still at the level of gathering and organizing materials and clinical data for analysis. There are no key findings to report at this time.

REPORTABLE OUTCOMES

There are no reportable outcomes at this time, given the early stage of the research project. Key accomplishments relate to organizational tasks that we have been able to complete. These posed a significant challenge due to the collaboration between two institutions required for the project.

CONCLUSIONS

We believe we are making excellent progress. This type of project often requires 1-2 years of organizational effort before actual molecular analyses can begin. We are well on track to begin this type of analysis in the next 6-12 months.

REFERENCES

None.

APPENDICES

None.